Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 45 Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Forty-fifth Meeting
23 April 2004

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
AQIS	Australian Quarantine Inspection Service
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
BP	British Pharmacopoeia
BPC	British Pharmaceutical Codex
BSE	Bovine spongiform encephalopathy
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicines Evaluation Committee
DSEB	Drug Safety and Evaluation Branch
ELF	Electronic Lodgement Facility
EP	European Pharmacopoeia
FSANZ	Food Safety Australia and New Zealand
LOAEL	Lowest Observable Adverse Effect Level
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
NOAEL	No Observable Adverse Effect Level
OCM	Office of Complementary Medicines
PBS	Pharmaceutical Benefits Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAL	Therapeutic Goods Administration Laboratory Branch
TSE	Transmissible spongiform encephalopathies

The forty-fifth meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in the Wangaratta Room, Hilton Melbourne Airport, Melbourne from 9.30 a.m. to 4.30 p.m. on Friday 23 April 2004.

Members of CMEC present were:

Associate Professor Heather Yeatman (Acting Chair)

Dr Vicki Kotsirilos
Associate Professor Douglas Moore
Professor Stephen Myers (item 5.1 onwards)
Dr John Ryan
Mr Kevin Ryan
Professor Gillian Shenfield
Dr Iggy Soosay (not present for items 6.1, 7.2, 9.1, 10.1, 10.2, 10.3 and 10.6)
Professor Bill Webster

Present from the Therapeutic Goods Administration (TGA) were:

Dr Fiona Cumming
Dr David Briggs
Dr John Hall
Dr John McEwen
Mr Karl Skewes

1. Procedural Matters

1.1 Opening of Meeting

The Acting Chair opened the meeting at 9.30 a.m. and welcomed CMEC Members and TGA staff.

1.2 Apologies

The Secretariat received apologies from Professor Tony Smith (Chair) who was overseas.

1.3 Conflict of Interest

Members submitted conflict of interest declarations specific to agenda items for this meeting to the Acting Chair.

2. Confirmation of Minutes of CMEC 44 (13 February 2004)

Members accepted the minutes of the forty-fourth meeting of CMEC as an accurate record of proceedings, subject to minor amendments.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 45.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 44, 13 February 2004), as amended, are a true and accurate record of that previous meeting.

3. Guidelines on levels and kinds of evidence to support claims for therapeutic goods (Guidelines)

CMEC did not consider any matters under this agenda item.

4. CMEC Working Party on Herbal Medicine Issues

CMEC did not consider any matters under this agenda item.

5. Action Arising from Previous Meetings

5.1 Iron phosphate – paediatrician response

Background
At meeting 43 of CMEC (November 2003), the Committee considered an application from an industry association to evaluate the suitability of iron phosphate (British Pharmaceutical Codex "BPC" 1973) for use a complementary medicine substance in Listed medicines via a 'switch' application. CMEC recommended that iron phosphate (BPC) was suitable for use as an ingredient in Listed medicines. However, CMEC made the recommendation subject to advice from a paediatric specialist on the potential for overdosing in children with iron phosphate and with Listable iron products more generally.

TGA sought this advice from a senior paediatric nutritionist in a School of Medicine at a major Australian university. The paediatric nutritionist noted that the majority of deaths from acute iron intoxication, occurred in children between 12 and 24 months of age. Due to the inquisitive nature of children at this age, the paediatric nutritionist suggested that limiting the pack size could be an important factor in reducing the potential for a small child to suffer from iron intoxication. For example, if the pack was not childproof and assuming a child consumed the

entire contents in the pack, then within the current scheduling requirements for Listed medicines, this would constitute a maximum dose of 750 mg of elemental iron. In a 10 kg one year old child, this maximum dose translates to a dose of 75 mg/kg body weight of elemental iron and in a 12 kg two year old child, 62.5 mg/kg body weight of elemental iron. Both of these doses are higher than the range of 20-60 mg/kg body weight noted as "potentially" toxic by the Queensland Poisons Information Centre. The paediatric nutritionist suggested that TGA consider reducing the total amount of iron contained in medicines to the "potentially" toxic rather than "definitely" toxic range by limiting the total amount of iron in products.

TGA has suggested that due to reasons such as poor palatability, texture, tablet or capsule size and quick detection by minders, that it would be unlikely that one to two year old children could consume an entire 750 mg pack of elemental iron. An assumption that a one year old child would not consume more than one-third of a 750 mg pack of elemental iron would result in a dose of approximately 25 mg/kg body weight of elemental iron. As per the advice from the Queensland Poisons Information Centre, this would be in the "potentially," rather than "definitely," toxic dose range. If combined with a limitation of the maximum pack size to 600 mg of elemental iron (as suggested by the paediatric nutritionist), the dose would be at or below 20 mg/kg body weight of elemental iron, for one and two year old children.

At present, sponsors must include all iron-containing preparations in child-resistant packaging, except where the unit dose is 5 mg or less or liquid forms containing 250 mg or less of iron.

Present discussion
Members discussed the potential costs to industry and costs and inconvenience to consumers by restricting the pack size of medicines containing iron phosphate (BPC) to ten tablet packs as suggested by the paediatric nutritionist. During the discussion, Members made the following comments:

- reduction in pack size would result in a significant cost to consumers;
- if necessary, consumers could obtain significantly larger pack sizes by prescription. Such a recommendation would not limit iron obtained by prescription but by those consumers who self-prescribe these supplements;
- consumers, with significant iron deficiency conditions should arguably be consulting with their healthcare practitioner; and,
- most prescribed iron supplements are also freely available over the counter in pharmacies.

A TGA officer remarked that limitation to this pack size would be a significant departure to the way that TGA has regulated Listed iron products in the past. Two Members both considered that it was a matter of relative toxicity and that these products should not be necessarily restricted to a smaller pack size but should be in child-resistant packaging.

Several Members raised the issue of iron phosphate celloid products, which had been previously discussed at meeting 43 of CMEC. Members had explained that these celloids contained 15 mg iron phosphate in each dose form, which constituted a total of 900 mg iron phosphate in each bottle. They do not have child-resistant packaging and these products are probably "grandfathered" registered products. A TGA officer noted that since each dose form represented

less than 5 mg of elemental iron it did not require child-resistant packaging. Members noted, however, that the entire package represented a potential risk for iron toxicity given the total iron content.

A Member questioned the bioavailability of iron from iron phosphate (BPC). A TGA officer noted that the evaluation report presented at meeting 43 of CMEC showed:

- 60 mg iron phosphate (BPC) could potentially deliver up to 19 mg of elemental iron; and,
- there was no data to establish how much elemental iron is actually absorbed by the consumer from iron phosphate (BPC) during digestion.

Another TGA officer commented that the bioavailability of iron phosphate (BPC) was less than other forms of iron. Further, TGA would have to provide appropriate evidence to support any requests for limitations on pack sizes or restrictions to child-proof packaging for Listed iron medicines to the other relevant committees within TGA. The Member then queried whether iron phosphate (BPC) represented a real risk in terms of the current dosage forms available and that bioavailability data would assist in the establishment of appropriate cut-off limits for child-resistant packaging of Listed medicines with iron phosphate (BPC). Another Member suggested that the Committee should not recommend the unrestricted use of an ingredient in Listed medicines based on cut-off points established by bioavailability alone when there was a real risk of adverse drug reactions and toxicity in children. The Acting Chair noted that the opinion of Members appeared to favour the use of child-resistant closures but with data to establish some cut-off levels below which this was not required.

One Member questioned why the advice from the paediatric nutritionist had not provided any real statistics relating to poisoning data in Australia. The Member also asked whether this was due to the States and Territories in Australia administering their own drugs and poisons legislation. A TGA officer explained that there was no national collection of poisoning data undertaken. Another Member suggested that TGA contact the Melbourne Children's' Hospital, as it had been compiling poisoning data in children. The first Member commented that poisons data would provide a useful point of reference, especially if recorded for the iron phosphate celloid products.

Members discussed the need for bioavailability and poisoning data to establish whether iron phosphate (BPC) or any other iron salts represented a real risk to consumers of Listed medicines. CMEC asked TGA to review this data and determine which Listed iron preparations may require child-proof packaging. A Member suggested that industry should provide this data and some opinion on this matter as well.

CMEC re-iterated it previous recommendation that iron phosphate (BPC) was suitable for use as an ingredient in Listed medicines. The Committee agreed that the review by TGA would address any future need for child-proof packaging of this ingredient or of other Listed iron products more generally.

CMEC Recommendation:
Members made the following recommendations:

Recommendation 45.2

CMEC recommends to TGA that iron phosphate (British Pharmaceutical Codex 1973) is suitable for use as an ingredient in Listed medicines.

Recommendation 45.3

CMEC further recommends to TGA that the need for child-resistant packaging for Listed iron products be reviewed.

5.2 Rutin – clarification on safety and adverse reactions associated with tri(hydroxyethyl) rutoside

Background
TGA previously presented Members with a safety review of rutin at CMEC 44 (February 2004). During discussion on this item, a Member commented on an article published in *the American Journal of Surgical Pathology* in 1989. The article described three cases in Switzerland of a rare disease, idiopathic entero-colic lymphoctyic phlebitis, which may have been associated with the consumption of a medicine (Venoruton) containing the substance, tri(hydroxyethyl) rutoside. The paper concluded:

> "Whether this association is fortuitous or reflects a pathogenetic role of the medication cannot be determined from our observations. None of our cases showed a symptomatology or laboratory findings that could be linked to a drug reaction."

Furthermore, in the 'note added in proof', the authors stated that re-challenge of one of the patients who had previously showed symptoms with Venoruton, was without clinical consequences. However, the Member was concerned that if tri(hydroxyethyl) rutoside was chemically identical to rutin, the safety review conducted on rutin might need reconsideration.

Members made the following recommendation:

> Recommendation 44.4
> CMEC noted the review of safety of rutin conducted by the TGA and recommends to TGA that it is suitable for use as an ingredient in listed medicines subject to clarification of the association between this substance and tri(hydroxyethyl) rutoside (which has been reported to be associated with adverse drug reactions).

TGA checked the chemical identities and concluded that rutin and tri(hydroxyethyl) rutoside were chemically distinct from each other and not likely to share the same toxicological properties. Adverse reactions potentially associated with tri(hydroxyethyl) rutoside have not been associated with rutin.

Present discussion
Members noted the explanation provided by TGA, establishing that rutin and tri-(hydroxyethyl)-rutoside were chemically distinct from each other and not likely to share the same toxicological properties. On this basis, CMEC agreed that rutin was suitable for use as an ingredient in Listed medicines.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 45.4

CMEC notes the review of safety of rutin conducted by the TGA and recommends to TGA that it is suitable for use as an ingredient in Listed medicines.

6. Evaluation of New Substances

6.1 *Leptospermum petersonii* (up to 5 %) oil

Background
TGA received an application to include *Leptospermum petersonii* oil for use as an excipient in topical Listed medicines, at concentrations of up to 5%. The sponsor indicated to TGA that it intends to use the oil as an excipient in particular head lice remedies.

In December 1998, CMEC recommended the use of *L. petersonii* oil as an excipient in topical Listed medicines in concentrations of up to 1%, subject to the sponsor supplying details of certain test method validation.

Characterisation
Production of *L. petersonii* oil involves steam distillation of *L. petersonii* leaves and twigs. The manufacturer sources *L. petersonii* leaves and twigs from a plantation located in northern New South Wales. There are four chemotypes of the *L. petersonii* tree and each has their own distinctive chemical compositions. Within each of these varieties there is also great variation in the concentrations of the constituent chemicals. The seven main constituents of *L. petersonii* oil are citral (the major constituent), citronellal, citronellol, geraniol, linalool, *alpha*-pinene and *beta*-pinene.

There are no specific monographs to describe *L. petersonii* oil. However, the sponsor has provided gas chromatographic analyses for three separate batches produced by the manufacturer. Results from these batch analyses will form the basis for a draft 'compositional guideline' to describe this ingredient.

History of therapeutic use
L. petersonii occurs naturally in northern NSW and in south-east Queensland. First reported in 1918, the oil was initially described as having a strong pleasant modified lemon odour suggestive of its principal constituents.

The dried leaves have been used to make tea. It has also been used as a fragrance raw material.

Furthermore, *L. petersonii* oil has been included as an ingredient in the following preparation types:

- insect (eg. mosquito) repellents;
- antiseptics;
- deodorisers in rooms or floral compositions;
- head lice treatments for humans (at 1 %);
- disinfectants;
- hydrosol for skin cleansing and throat gargle;
- dermal products to treat mange and fleas in dogs; and,
- aromatic blends for oil burners to assist in the treatment of coughs and colds.

Aromatherapy industry sources recommend that *L. petersonii* oil should not be applied to skin at concentrations greater than 2.5% because of its high citral content.

Regulatory status
The use of the various components of the oil when used as flavours or fragrances are subject to a number of national legislated standards which control the concentrations used in food or their use in cosmetics. Many of the major constituents are restricted in their use or concentration in cosmetics. The seven major constituents of *L. petersonii oil* have USA FDA Generally Regarded As Safe (GRAS) Status as food additives. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has classified citronellal and geraniol at current intake rates as of 'no safety concern'. JECFA has established a group ADI of 0.0 - 0.5 mg/kg body weight expressed as citral, for citral, citronellol, geranyl acetate, linalool and linalyl acetate.

Pharmacology
The pharmacology and toxicology assessment has also been assisted by reference to other essential oils with similar constituent profiles to *L. petersonii* oil.

Due to the intended role of this excipient in topical Listed medicines, the TGA evaluation took the view that dermal absorption was the more important pharmacokinetic parameter from a safety point of view. Based on studies with the main constituent, citral, dermal absorption appeared to be slow and incomplete. Further, results obtained with related oils, showed that very limited amounts of citral were absorbed into discs of human skin *in vitro*. The extent of dermal absorption of citral was considerably curtailed when present in an essential oil compared to citral alone. Studies on the biotransformation of citral in rats showed that following absorption it distributed widely and was then rapidly and completely metabolised and excreted. There was no evidence of toxic metabolites, major tissue depot or accumulation of citral in the body. Urine

was the major route of excretion of the citral metabolites followed by biliary excretion and exhaled excretion.

Apart from differences to citral in biotransformation, results of various studies showed that the other major constituents of *L. petersonii* oil were similarly disposed in terms of absorption, distribution and excretion. The only exception was for the pinenes, which had a longer half-life in poorly perfused tissues suggesting a higher affinity for adipose tissue.

Pharmacokinetic consequences
In respect of a topical formulation containing *L. petersonii* oil at 5%, it would be unlikely that the ingestion, vapour inhalation or dermal application of this formulation would result in significant absorption of citral or other constituents of *L. petersonii* oil. Any amounts absorbed are not likely to cause systemic toxicity or be beyond the capacity of the body to metabolise and excrete quickly.

Toxicology
TGA considered that *L. petersonii* oil at 5 % has low acute oral and dermal toxicity. The acute oral LD_{50} of *L. petersonii* oil in rats was calculated to be 4880 mg/kg body weight. The acute dermal LD_{50} of *L. petersonii* oil in rabbits was calculated to be greater than 2850 mg/kg body weight. There was no explanation for the lower dermal LD_{50} in rabbits compared with the oral toxicity in rats. There have been no acute inhalation toxicity studies conducted for the oil.

Details of local tolerance studies were submitted by the sponsor for *L. petersonii* oil at concentrations of 5% (human open patch test skin irritation/sensitisation evaluation) and 10% (*in vitro* dermal and ocular irritection® studies). At a 10% concentration the oil was a minimal irritant in the ocular simulation test system used. At 10% the oil was non-irritant in the dermal simulation test system used. *L. petersonii* oil at 5% was a non-primary irritant and a non-primary sensitiser to human skin in the test system used. Qualitative and quantitative histological studies showed that the skin sensitisation capacity of citral was modulated by *d*-limonene. None of the other major constituents of *L. petersonii* are known skin sensitisers except that oxidised *alpha*-pinene has caused sensitisation in humans.

Respiratory tract irritation studies in rats indicated that at 5% the oil was unlikely to result in human exposure to an atmosphere of citral sufficient cause respiratory irritation. Gastrointestinal mucosa irritation by a formulation containing *L. petersonii* oil at 5% was unlikely in view of its lack of irritancy to skin and mild ocular irritancy.

There were no repeat-dose, sub-chronic or chronic toxicity studies in animals found for *L. petersonii* oil. The evaluation report contained a review of the studies available for some of the constituents. The report concluded that the use of a formulation containing *L. petersonii* oil at 5%, was unlikely to result in the degree, duration or frequency of exposure utilised in sub-acute animal tests. Any toxicity due to the constituents of the oil demonstrated by these tests was unlikely to be experienced by consumers of a topical product containing the oil at concentrations up to 5 %.

There were no reports of carcinogenicity, genotoxicity or reproductive studies with *L. petersonii* oil but studies on the main constituents were also reviewed in the evaluation report. There was no evidence that a formulation containing *L. petersonii* oil at 5% would be carcinogenic because of the presence of the oil, at the degree, duration and routes of human exposure likely to result from its use in humans. The only positive genotoxicity finding reported in many studies was that citral induced sister chromatid exchange in Chinese hamster ovary cells *in vitro* with and without metabolic activation. Human exposure to a formulation containing *L. petersonii* oil at 5% at the doses, frequency and timing required to affect reproductive parameters was highly unlikely.

There was some information presented as to the cytotoxicity of the various components in the oil and these have been used to provide an indication of the no observable adverse effect level (NOAEL) in humans. As an extrapolation from the cytotoxicity determinations of lemon myrtle oil, it was concluded that a 60 kg person or a 10 kg child may consume orally 700 mL or 120 mL respectively of a formulation containing *L. petersonii* oil at 5% without adverse effect being attributable to the oil.

There were no reports of human poisoning found for *L. petersonii* oil.

Clinical data
There were no clinical data available for *L. petersonii* oil.

Adverse reactions
No adverse reactions to *L. petersonii* have been reported.

TGA also submitted comments from one of the CMEC Expert Advisers with expertise in aromatherapy for CMEC consideration.

Present discussion
Before commencing discussion on this item, the Acting Chair clarified for Members that the application was for use of *L. petersonii* oil as an excipient ingredient in topical Listed medicines, at concentrations of up to 5%.

One Member commented there did not appear to be any significant toxicity concerns for *L. petersonii* oil at concentrations of up to 5 % and noted the following observations from the evaluation report:

- skin studies did not appear to display any irritant or sensitisation properties;
- absorption of *L. petersonii* oil did occur through the skin but if used in a shampoo formulation, the contact would not be long;
- the oil did not appear to be an irritant to the eyes;
- *L. petersonii* oil had inhalation effects at high concentrations. At concentrations of up to 5 %, these effects would probably be insignificant;
- the LD_{50} was very high, which meant that *L. petersonii* oil was a relatively non-toxic substance if consumed orally; and,

- two-year studies of carcinogenicity and mutagenicity on mice using citral did not reveal any significant findings.

The Member remarked that overall, the toxicological profile of *L. petersonii* oil at the proposed concentration of up to 5 %, appeared to be relatively benign. Two Members then discussed the potential for absorption of *L. petersonii* oil into the scalp given the vascular nature of this area. One Member conceded that there was no evidence on the metabolism of the oil via this topical route but the evidence suggested it was relatively inert.

The Acting Chair noted a concern expressed by the CMEC Expert Adviser in relation to the potential for *L. petersonii* oil to have inhalation effects in children. Several Members agreed that at concentrations of up to 5 % in Listed topical medicine formulations, it represented a low risk for this effect.

One TGA officer referred to two dermatological studies in the evaluation report that used *L. petersonii* oil. Each study used a different base cream in the application of the *L. petersonii* oil. One was an *in vitro* test performed in Australia while the other used a modified patch test study on fifty adult humans in the United States of America. There was little information provided in the studies on the potential irritancy of the base creams used in the studies. The TGA officer suggested that in effect, there is an element of trust assumed from the results of these two studies.

A Member questioned the role of *L. petersonii* oil as an excipient at concentrations of up to 5 % rather than at concentrations of up to 1 % in topical products, as previously recommended by CMEC. Another Member commented that many of the active ingredients in head lice treatment products frequently had pungent odours and that the fragrance from *L. petersonii* oil would certainly mask many of these odours. If the Committee recommended the suitability of *L. petersonii* oil at concentrations of up to 5 % as an excipient in topical Listed medicines, it would limit the use of this ingredient to fragrance purposes alone.

Members unanimously agreed to recommend that *L. petersonii* oil at concentrations of up to 5 % was suitable for use as an excipient in topical Listed medicines.

CMEC Recommendation:
Members made the following recommendation:

Recommendation 45.5

CMEC recommends to TGA that *Leptospermum petersonii* oil is suitable for use as an excipient ingredient up to 5% concentration in Listable topical medicines only.

7. Safety or Efficacy Reviews120

7.1 Safety review: Glucosamine

Background
At meeting 35 of CMEC (June 2002), Members asked TGA to conduct a safety review in relation to the potential effect that glucosamine may have on clotting (and other blood parameters) alone or in combination with other medicines such as warfarin. The review was initially suggested by the Adverse Drug Reactions Committee (ADRAC) at meeting 260, due to the accumulating number of adverse reaction reports recorded in the ADRAC database.

TGA engaged the services of a clinical evaluator to assist in the completion of the safety review. The clinical evaluator examined adverse drug reaction reports received by TGA, adverse drug reaction reports recorded in the World Health Organisation database and papers from a comprehensive literature search on glucosamine and adverse drug reactions.

The clinical evaluator reached the following conclusions about the safety of glucosamine:

- The most common adverse drug reactions seen in Australia were allergic reactions, eg. skin reactions and oedema;
- The second most common reactions were gastrointestinal, eg. abdominal pain, nausea and diarrhoea;
- There was no long term safety data available for glucosamine;
- There have been a small number of reports of bleeding but the reports were complicated by other medical conditions. There was no consistency of the bleeding and no association with any particular product; and
- There was no information in the literature that suggested a problem with haematological parameters associated with the administration of glucosamine.

Present discussion
A Member observed that, although the number of reports was low, the severity of adverse reactions recorded for glucosamine sulphate appeared to be more severe and systemic. The Member questioned whether there was a trend in severity associated with the consumption glucosamine sulphate, possibly even due to the presence of sulphur. A second Member commented that the number of reviewed reactions was not sufficient to show any specific trends. High utilisation tended to correspond with increased reports of adverse drug reactions. The second Member noted that the adverse drug reactions for all forms of glucosamine do not appear to display any specific associations, other than abdominal complaints and allergic reactions. These sorts of reactions are within the limits for an unpredictable allergic reaction of a popularly consumed medicine. A third Member remarked that sulphur allergies normally arise from exposed sulphur groups and not from sulphates. This Member suggested that broad formulation differences or the quality of the glucosamine sulphate used as an ingredient might cause some of the reactions that the first Member commented about, especially if it contained more of the shellfish base. Other than abdominal complaints and unpredictable allergic reactions, there did not appear to be any particular trends in the adverse drug reactions reviewed. The third Member noted that there had been additional reports recording an interaction with warfarin (increased INR) & rectal bleeding.

One Member suggested that the quality of glucosamine supplied in Australia also appeared to be an unresolved issue. An evaluation report submitted to CMEC in 1998 revealed that the method for analysis was relatively non-specific. Given that many manufacturers source glucosamine from seafood sources, the Member stated that the compositional guideline should incorporate a more detailed analysis such as HPLC to assist in the determination and setting of limits of any impurities or contaminants. Another Member questioned whether a sponsor could utilise an alternative technique such as electrophoresis, to differentiate the different forms of glucosamine and their impurity levels. A TGA officer noted that TGA could review the current compositional guidelines and monograph for glucosamine. Further, the officer commented that the impurity levels would clearly depend on the source of glucosamine and TGA would need to build these different levels into the final monograph. However, the establishment of these limits would not necessarily have any impact on the number of adverse drug reaction reports.

Another Member commented that a Canadian report in 2000 reported an increase in INR when glucosamine was administered to patients receiving warfarin. The INR decreased upon cessation of glucosamine to the patients. Although there were no details of how many patients participated in the study, the result appeared to be relatively specific but did not appear in the safety review. The Member also noted that heparin contained glucosamine residues and questioned whether the residues contributed to the anticoagulant activity of heparin. Because both heparin and heparan sulfate contained glucosamine moieties, this has lead to concern about the potential anticoagulant activity of glucosamine in the literature but did not appear to be adequately addressed in the safety review. Another Member believed that ADRAC had previously noted a possible association between glucosamine and warfarin as a cause of increased bleeding time and reported this association in a previous ADRAC Bulletin. The Acting Chair asked TGA to check if ADRAC had released a Bulletin with comments to that effect. In the absence of an ADRAC Bulletin article, the Acting Chair requested that ADRAC consider providing comment on the possible association between glucosamine and warfarin in a forthcoming Bulletin.

A Member questioned how widely used glucosamine products were in Australia. The Member suggested that usage figures would assist in the determination of whether the number of adverse drug reaction reports were significant or not. For example, one particular brand appeared in a number of adverse drug reaction reports in the safety review. A TGA officer mentioned that TGA could ask (while maintaining confidentiality) for market-share data directly from the company if necessary. A second Member also noted that most of the major companies kept market-share reports. A second TGA officer suggested that TGA could also request chromatographic profiles of the glucosamine used in their products, which could provide some information on the potential contamination and/or impurity differences between glucosamine hydrochloride and glucosamine sulfate. The second Member noted that most of the glucosamine was probably sourced from the Peoples Republic of China where only limited quality profiling of this ingredient may be undertaken.

On the basis of the information presented in the safety review Members did not consider that any regulatory intervention was required.

CMEC Recommendation:

Members made the following recommendation:

Recommendation 45.6

CMEC notes a review of Australian adverse drug reaction data for glucosamine conducted by the TGA and recommends to TGA that glucosamine continues to be suitable for use as an ingredient in Listed medicines.

7.2 – 7.3 CMEC considered two items and made one recommendation on each item to the TGA.

8. Registration Applications

CMEC did not consider any matters under this agenda item.

9. Variation to a Registered Product

9.1 CMEC considered one item and made one recommendation to the TGA.

10. Matters referred from within the TGA

10.1 Adverse Drug Reaction Advisory Committee report (ADRAC) Meeting 274

A member introduced item 10.1 to the Committee.

Members noted the adverse drug reaction reports from 274th meeting of ADRAC.

10.2 – 10.6 CMEC considered five items and made two recommendations to the TGA

11. Recommendation record

Item 2 Minutes of CMEC's 44th. Meeting

Recommendation 45.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 44, 13 February 2004), as amended, are a true and accurate record of that previous meeting.

Item 5.1 Action Arising from Previous Meetings – Application for the Evaluation of a New Substance: Iron Phosphate (British Pharmaceutical Codex 1973)

Recommendation 45.2

CMEC recommends to TGA that iron phosphate (British Pharmaceutical Codex 1973) is suitable for use as an ingredient in Listed medicines.

Recommendation 45.3

CMEC further recommends to TGA that the need for child-resistant packaging for Listed iron products be reviewed.

Item 5.2 Action Arising from Previous Meetings – Safety Review: Rutin

Recommendation 45.4

CMEC notes the review of safety of rutin conducted by the TGA and recommends to TGA that it is suitable for use as an ingredient in Listed medicines.

Item 6.1 Application for the Evaluation of a New Substance: *Leptospermum petersonii* oil (up to 5 %)

Recommendation 45.5

CMEC recommends to TGA that *Leptospermum petersonii* oil is suitable for use as an excipient ingredient up to 5% concentration in Listable topical medicines only.

Item 7.1 Safety Review: Glucosamine

Recommendation 45.6

CMEC notes a review of Australian adverse drug reaction data for glucosamine conducted by the TGA and recommends to TGA that glucosamine continues to be suitable for use as an ingredient in Listed medicines.

12. For Information

CMEC did not consider any matters under this agenda item.

13. Other business

There was no other business for consideration by CMEC.

The Chair closed the meeting at 4.30 p.m.